CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

75046

APPROVAL LETTER

ANDA 75-046

AUG 12 1998

Bedford Laboratories
Attention: Shahid Ahmed
270 Northfield Road
Bedford, Ohio 44146

Dear Sir:

This is in reference to your abbreviated new drug application dated December 30, 1996, submitted pursuant to Section 505(j) of the Federal Food, Drug, and Cosmetic Act, for Butorphanol Tartrate Injection USP, 2 mg/mL, 10 mL multiple dose vials.

Reference is also made to your amendments dated April 2, June 12 and June 30, July 8, 13 and 17, 1998.

We have completed the review of this abbreviated application and have concluded that the drug is safe and effective for use as recommended in the submitted labeling. Accordingly, the application is approved. The Division of Bioequivalence has determined your Butorphanol Tartrate Injection USP,2 mg/mL, 10 mL multiple dose vials to be bioequivalent and, therefore, therapeutically equivalent to the listed drug (Stadol® Injection, 2 mg/mL of Apothecon Inc.).

Under 21 CFR 314.70, certain changes in the conditions described in this abbreviated application require an approved supplemental application before the change may be made.

Post-marketing reporting requirements for this abbreviated application are set forth in 21 CFR 314.80-81 and 314.98. The Office of Generic Drugs should be advised of any change in the marketing status of this drug.

We request that you submit, in duplicate, any proposed advertising or promotional copy which you intend to use in your initial advertising or promotional campaigns. Please submit all proposed materials in draft or mock-up form, not final print. Submit both copies together with a copy of the proposed or final

printed labeling to the Division of Drug Marketing, Advertising, and Communications (HFD-240). Please do not use Form FD-2253 (Transmittal of Advertisements and Promotional Labeling for Drugs for Human Use) for this initial submission.

We call your attention to 21 CFR 314.81(b)(3) which requires that materials for any subsequent advertising or promotional campaign be submitted to our Division of Drug Marketing, Advertising, and Communications (HFD-240) with a completed Form FD-2253 at the time of their initial use.

Sincerely yours,

/S/ 8/11/98

Douglas L. Sporn
Director
Office of Generic Drugs
Center for Drug Evaluation and Research

CENTER FOR DRUG EVALUATION AND RESEARCH

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DRAFT FINAL PRINTED LABELING

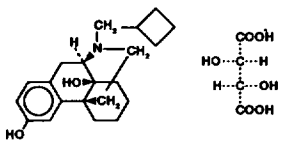
BEDFORD LABORATORIES

Cv

BUTORPHANOL TARTRATE INJECTION USP

DESCRIPTION

Butorphanol tartrate is a synthetically derived opioid agonist-antagonist analgesic of the phenanthrene series. The chemical name is (-)-17-(Cyclobutylmethyl)morphinan-3,14-diol D-(-)-tartrate(1:1)(salt). The molecular formula is $C_{21}H_{29}NO_2 \cdot C_4H_6O_6$, which corresponds to a molecular weight of 477.56 and the following structural formula:



Butorphanol tartrate is a white crystalline substance. The dose is expressed as the tartrate salt. One milligram of the salt is equivalent to 0.68 mg of the free base. The n-octanol/aqueous buffer partition coefficient of butorphanol is 180:1 at pH 7.5.

Butorphanol tartrate injection is a sterile, parenteral, aqueous solution of butorphanol tartrate for intravenous or intramuscular administration. In addition to 1 or 2 mg of butorphanol tartrate, each mL of solution contains 3.3 mg of citric acid, 6.4 mg sodium citrate, and 6.4 mg sodium chloride, and 0.1 mg benzethonium chloride (in multiple dose vial only) as a preservative. The pH range is 3.5 to 5.0.

CLINICAL PHARMACOLOGY

General Pharmacology and Mechanism of Action

Butorphanol is a mixed agonist-antagonist with low intrinsic activity at receptors of the μ-opioid type (morphine-like). It is also an agonist at k-opioid receptors.

Its interactions with these receptors in the central nervous system apparently mediate most of its pharmacologic effects, including analgesia.

In addition to analgesia, CNS effects include depression of spontaneous respiratory activity and cough, stimulation of the emetic center, miosis and sedation. Effects possibly mediated by non-CNS mechanisms include alteration in cardiovascular resistance and capacitance, bronchomotor tone, gastrointestinal secretory and motor activity and bladder sphincter activity.

In an animal model, the dose of butorphanol tartrate required to antagonize morphine analgesia by 50% was similar to that for nalorphine, less than that for pentazocine and more than that for naloxone.

The pharmacological activity of butorphanol metabolites has not been studied in humans; in animal studies, butorphanol metabolites have demonstrated some analgesic activity.

In human studies of butorphanol (see **Clinical Trials**), sedation is commonly noted at doses of 0.5 mg or more. Narcosis is produced by 10 to 12 mg doses of butorphanol administered over 10 to 15 minutes intravenously.

Butorphanol, like other mixed agonist-antagonists with a high affinity for the kappa receptor, may produce unpleasant psychotomimetic effects in some individuals.

Nausea and/or vomiting may be produced by doses of 1 mg or more administered by any route.

In human studies involving individuals without significant respiratory dysfunction, 2 mg of butorphanol IV and 10 mg of morphine sulfate IV depressed respiration to a comparable degree. At higher doses, the magnitude of respiratory depression with butorphanol is not appreciably increased; however, the duration of respiratory depression is longer. Respiratory depression noted after administration of butorphanol to humans by any route is reversed by treatment with naloxone, a specific opioid antagonist (see **Treatment** in **OVERDOSAGE**).

Butorphanol tartrate demonstrates antitussive effects in animals at doses less than those required for analgesia.

Hemodynamic changes noted during cardiac catheterization in patients receiving single 0.025 mg/kg intravenous doses of butorphanol have included increases in pulmonary artery pressure, wedge pressure and vascular resistance, increases in left ventricular end diastolic pressure and in systemic arterial pressure.

Pharmacodynamics

The analgesic effect of butorphanol is influenced by the route of administration. Onset of analgesia is within a few minutes for intravenous administration, within 15 minutes for intramuscular injection.

Peak analgesic activity occurs within 30 to 60 minutes following intravenous and intramuscular administration.

The duration of analgesia varies depending on the pain model as well as the route of administration, but is generally 3 to 4 hours with IM and IV doses as defined by the time 50% of the patients required remedication. In postoperative studies, the duration of analgesia with IV or IM butorphanol was similar to morphine, meperidine and pentazocine when administered in the same fashion at equipotent doses (see **Clinical Trials**).

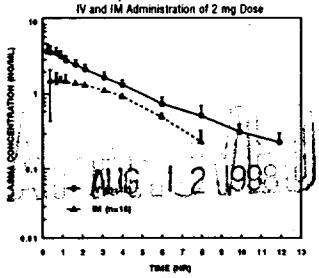
Pharmacokinetics

Butorphanol tartrate is rapidly absorbed after IM injection and peak plasma levels are reached in 20 to 40 minutes.

Following its initial absorption/distribution phase, the single dose pharmacokinetics of butorphanol by the intravenous and intramuscular routes of administration are similar (see **Figure** 1).

Figure 1

Butorphanol Plasma Levels After IV and IM Administration of 2 mg Dose



Serum protein binding is independent of concentration over the range achieved in clinical practice (up to 7 ng/mL) with a bound fraction of approximately 80%.

The volume of distribution of butorphanol varies from 305 to 901 liters and total body clearance from 52 to 154 liters/hr (see **Table 1**).

Table 1 - Mean Pharmacokinetic Parameters of Butorphanol in Young and Elderly Subjects[a]

Parameters	Young	Elderly
AUC (inf)[b] (hr.ng/mL)	7.24 (1.57) (4.40-9.77)	8.71 (2.02) (4.76-13.03)
Half-life (hr)	4.56 (1.67) (2.06-8.70)	5.61 (1.36) (3.25-8.79)
Volume of Distribution[c] (L)	487 (155) (305-901)	552 (124) (305-737)
Total Body Clearance (L/hr)	99 (23) (70-154)	82 (21) (52-143)

a) Young subjects (n=24) are from 20 to 40 years old and elderly (n=24) are greater than 65 years of age.

b) Area under the plasma concentration-time curve after a 1 mg dose.

c) Derived from IV data.

The drug is transported across the blood brain and placental barriers and into human milk (see **Labor and Delivery**, and **Nursing Mothers** under **PRECAUTIONS**).

Butorphanol is extensively metabolized in the liver. Metabolism is qualitatively and quantitatively similar following intravenous or intramuscular administration. Oral bioavailability is only 5 to 17% because of extensive first pass metabolism of butorphanol.

The major metabolite of butorphanol is hydroxybutorphanol, while norbutorphanol is produced in small amounts. Both have been detected in plasma following administration of butorphanol, with norbutorphanol present at trace levels at most time points. The elimination half-life of hydroxybutorphanol is about 18 hours and as a consequence considerable accumulation occurs when butorphanol is dosed to steady state.

Elimination occurs by urine and fecal excretion. When ^3H labeled butorphanol is administered to normal subjects, most (70 to 80%) of the dose is recovered in the urine, while approximately 15% is recovered in the feces.

About 5% of the dose is recovered in the urine as butorphanol. Forty-nine percent is eliminated in the urine as hydroxybutorphanol. Less than 5% is excreted in the urine as norbutorphanol (see also **CLINICAL PHARMACOLOGY** above).

Butorphanol pharmacokinetics in the elderly differ from younger patients (see **Table 1**).

In renally impaired patients with creatinine clearances <30 mL/min the elimination half-life is approximately doubled and the total body clearance is approximately one-half (10.5 hours [clearance 150 L/h] as compared to 5.8 hours [clearance 260 L/h] in normals). No effect was observed on Cmax or Tmax after a single dose.

For further recommendations refer to statements on use in **Geriatric Patients, Hepatic Disease, Renal Disease,** and statement on **Drug Interactions** in the **PRECAUTIONS** section, and **Individualization of Dosage** below.

Clinical Trials

The effectiveness of opioid analgesics varies in different pain syndromes. Studies with butorphanol tatrate injection have been performed in postoperative (primarily abdominal and orthopedic) pain and pain during labor and delivery, as preoperative and preanesthetic medication, and as a supplement to balanced anesthesia (see below).

Use in the Management of Pain

Postoperative Pain: The analgesic efficacy of butorphanol tartrate injection in postoperative pain was investigated in several double-blind active-controlled studies involving 958 butorphanol-treated patients. The following doses were found to have approximately equivalent analgesic effect: 2 mg butorphanol, 10 mg morphine, 40 mg pentazocine, and 80 mg meperidine.

After intravenous administration of butorphanol tartrate, onset and peak analgesic effect occurred by the time of first observation (30 minutes). After intramuscular administration, pain relief onset occurred at 30 minutes or less, and peak effect occurred between 30 minutes and one hour. The duration of action of butorphanol tartrate injection was 3 to 4 hours when defined as the time necessary for pain intensity to return to pretreatment level or the time to retreatment.

Preanesthetic Medication: Butorphanol tartrate injection (2 mg and 4 mg) and meperidine (80 mg) were studied for use as preanesthetic medication in hospitalized surgical patients. Patients received a single intramuscular dose of either butorphanol or meperidine approximately 90 minutes prior to anesthesia. The anesthesia regimen included barbiturate induction, followed by nitrous oxide and oxygen with halothane or enflurane, with or without a muscle relaxant.

Anesthetic preparation was rated as satisfactory in all 42 butorphanol tartrate patients regardless of the type of surgery.

Balanced Anesthesia: Butorphanol tartrate administered intravenously (mean dose 2 mg) was compared to intravenous morphine sulfate (mean dose 10 mg) as premedication shortly before thiopental induction, followed by balanced anesthesia in 50 ASA Class 1 and 2 patients. Anesthesia was then maintained by repeated intravenous doses, averaging 4.6 mg butorphanol tartrate and 22.8 mg morphine per patient.

Anesthetic induction and maintenance were generally rated as satisfactory with both butorphanol tartrate (25 patients) and morphine (25 patients) regardless of the type of surgery performed. Emergence from anesthesia was comparable with both agents.

Labor (see **PRECAUTIONS**): The analgesic efficacy of IV butorphanol tartrate was studied in pain during labor. In a total of 145 patients butorphanol tartrate (1 mg and 2 mg) was as effective as 40 mg and 80 mg of meperidine (144 patients) in the relief of pain in labor with no effect on the duration or progress of labor. Both drugs readily crossed the placenta and entered fetal circulation. The condition of the infants in these studies, determined by Apgar scores at 1 and 5 minutes (8 or above) and time to sustained respiration, showed that butorphanol tartrate had the same effect on the infants as meperidine.

In these studies neurobehavioral testing in infants exposed to butorphanol tartrate at a mean of 18.6 hours after delivery, showed no significant differences between treatment groups.

Individualization of Dosage

Use of butorphanol in geriatric patients, patients with renal impairment, patients with hepatic impairment, and during labor requires extra caution (see below and the appropriate sections in **PRECAUTIONS**).

For pain relief the recommended initial dosage regimen of butorphanol tartrate injection is 1 mg IV or 2 mg IM with repeated doses every 3 to 4 hours, as necessary. This dosage regimen is likely to be effective for the majority of patients. Dosage adjustments of butorphanol tartrate should be based on observations of its beneficial and adverse effects. The initial dose in the elderly and in patients with renal or hepatic impairment should generally be half the recommended adult dose (0.5 mg IV and 1 mg IM). Repeat doses in these patients should be determined by the patient's response rather than at fixed intervals but will generally be no less than 6 hours (see **PRECAUTIONS**).

The usual preoperative dose is 2 mg IM given 60 to 90 minutes before surgery or 2 mg IV shortly before induction. This is approximately equivalent in sedative effect to 10 mg morphine or 80 mg of meperidine. This single preoperative dose should be individualized based on age, body weight, physical status, underlying pathological condition, use of other drugs, type of anesthesia to be used and the surgical procedure involved.

During maintenance in balanced anesthesia the usual incremental dose of butorphanol tartrate is 0.5 mg to 1 mg IV. The incremental dose may be higher, up to 0.06 mg/kg (4 mg/70 kg), depending on previous sedative, analgesic, and hypnotic drugs administered. The total dose of butorphanol tartrate will vary; however, patients seldom require less than 4 mg or more than 12.5 mg (approximately 0.06 to 0.18 mg/kg).

As with other opioids of this class, butorphanol tartrate may not provide adequate intraoperative analgesia in every patient or under all conditions. A failure to achieve successful analgesia during balanced anesthesia is commonly reflected by increases in general sympathetic tone. Consequently, if blood pressure or heart rate continue to rise, consideration should be given to adding a potent volatile liquid inhalation anesthetic or another intravenous medication.

In labor, the recommended initial dose of butorphanol tartrate is 1 mg or 2 mg IM or IV in mothers with fetuses of 37 weeks gestation or beyond and without signs of fetal distress. Dosage adjustments of butorphanol tartrate in labor should be based on initial response with consideration given to concomitant analgesic or sedative drugs and the expected time of delivery. A dose should not be repeated in less than four hours nor administered less than four hours prior to anticipated delivery (see **PRECAUTIONS**).

INDICATIONS AND USAGE

Butorphanol tartrate injection is indicated for the management of pain when the use of an opioid analgesic is appropriate.

Butorphanol tartrate injection is also indicated as preoperative or preanesthetic medication, as a supplement to balanced anesthesia, and for the relief of pain during labor.

CONTRAINDICATIONS

Butorphanol tartrate injection is contraindicated in patients hypersensitive to butorphanol tartrate or the preservative benzethonium chloride in the multiple dose vial.

WARNINGS

Patients Dependent on Narcotics

Because of its opioid antagonist properties, butorphanol is not recommended for use in patients dependent on narcotics. Such patients should have an adequate period of withdrawal from opioid drugs prior to beginning butorphanol therapy. In patients taking opioid analgesics chronically, butorphanol has precipitated withdrawal symptoms such as anxiety, agitation, mood changes, hallucinations, dysphoria, weakness and diarrhea.

Because of the difficulty in assessing opioid tolerance in patients who have recently received repeated doses of narcotic analgesic medication, caution should be used in the administration of butorphanol to such patients.

Drug Abuse

All routes of administration of butorphanol tartrate have been associated with episodes of abuse, with most reports involving outpatient treatment of chronically painful conditions. Of the cases received, there were more reports of abuse with the nasal spray formulation than with the formulation administered parenterally. In general, patients receiving opioid treatment for an extended period of time are at a higher risk for abuse.

Drug Dependence, Tolerance and Withdrawal

Prolonged use of butorphanol tartrate for the treatment of chronically painful conditions may also result in dependence. The development of dependence may be marked by tolerance (a decrease in response to a given dose) which may lead to non-medical dose escalation and craving, or drug seeking behavior. Abrupt cessation of use by dependent patients may result in symptoms of withdrawal.

Proper patient selection, dose and prescribing limitations, appropriate directions for use, and frequent monitoring are important to minimize the risk of abuse and dependence. (See **DRUG ABUSE AND DEPENDENCE** section below.)

PRECAUTIONS

Head Injury and Increased Intracranial Pressure

As with other opioids, the use of butorphanol in patients with head injury may be associated with carbon dioxide retention and secondary elevation of cerebrospinal fluid pressure, drug-induced miosis, and alterations in mental state that would obscure the interpretation of the clinical course of patients with head injuries. In such patients, butorphanol should be used only if the benefits of use outweigh the potential risks.

Disorders of Respiratory Function or Control
Butorphanol may produce respiratory depression, especially in patients receiving other CNS active agents, or patients suffering from CNS diseases or respiratory impairment.

Hepatic and Renal Disease
In patients with severe hepatic or renal disease the initial dosage interval for butorphanol tartrate should be increased to 6 to 8 hours until the response has been well characterized. Subsequent doses should be determined by patient response rather than being scheduled at fixed intervals (see **CLINICAL PHARMACOLOGY, Individualization of Dosage**).

Cardiovascular Effects
Because butorphanol may increase the work of the heart, especially the pulmonary circuit (see **CLINICAL PHARMACOLGY**), the use of butorphanol in patients with acute myocardial infarction, ventricular dysfunction, or coronary insufficiency should be limited to those situations where the benefits clearly outweigh the risk.

Severe hypertension has been reported rarely during butorphanol therapy. In such cases, butorphanol should be discontinued and the hypertension treated with antihypertensive drugs. In patients who are not opioid dependent, naloxone has also been reported to be effective.

Use in Ambulatory Patients
1. Opioid analgesics, including butorphanol, impair the mental and physical abilities required for the performance of potentially dangerous tasks such as driving a car or operating machinery. Effects such as drowsiness or dizziness can appear, usually within the first hour after dosing. These effects may persist for varying periods of time after dosing. Patients who have taken butorphanol should not drive or operate dangerous machinery for at least 1 hour and until the effects of the drug are no longer present.

2. Alcohol should not be consumed while using butorphanol. Concurrent use of butorphanol with drugs that affect the central nervous system (e.g., alcohol, barbiturates, tranquilizers, and antihistamines) may result in increased central nervous system depressant effects such as drowsiness, dizziness and impaired mental function.

3. This is one of a class of drugs known to be abused and thus should be handled accordingly.

Drug Interactions
Concurrent use of butorphanol with central nervous system depressants (e.g., alcohol, barbiturates, tranquilizers, and antihistamines) may result in increased central nervous system depressant effects. When used concurrently with such drugs, the dose of butorphanol should be the smallest effective dose and the frequency of dosing reduced as much as possible when administered concomitantly with drugs that potentiate the action of opioids.

It is not known if the effects of butorphanol are altered by concomitant medications that affect hepatic metabolism of drugs (erythromycin, theophylline, etc.), but physicians should be alert to the possibility that a smaller initial dose and longer intervals between doses may be needed.

No information is available about the use of butorphanol concurrently with MAO inhibitors.

Information for Patients
See **Use in Ambulatory Patients** above.

Carcinogenesis, Mutagenesis, Impairment of Fertility
Two year carcinogenicity studies were conducted in mice and rats given butorphanol tartrate in the diet up to 60 mg/kg/day (180 mg/m² for mice and 354 mg/m² for rats). There was no evidence of carcinogenicity in either species in these studies.

Butorphanol was not genotoxic in *S. typhimurium* or *E. coli* assays or in unscheduled DNA synthesis and repair assays conducted in cultured human fibroblast cells.

Rats treated orally with 160 mg/kg/day (944 mg/m²) had reduced pregnancy rate. However, a similar effect was not observed with a 2.5 mg/kg/day (14.75 mg/m²) subcutaneous dose.

Pregnancy, Teratogenic Effects: Pregnancy Category C
Reproduction studies in mice, rats and rabbits during organogenesis did not reveal any teratogenic potential to butorphanol. However, pregnant rats treated subcutaneously with butorphanol at 1 mg/kg (5.9 mg/m²) had a higher frequency of stillbirths than controls. Butorphanol at 30 mg/kg/oral (5.1 mg/m²) and 60 mg/kg/oral (10.2 mg/m²) also showed higher incidences of post-implantation loss in rabbits.

There are no adequate and well-controlled studies of butorphanol tartrate in pregnant women before 37 weeks of gestation. Butorphanol tartrate injection should be used during pregnancy only if the potential benefit justifies the potential risk to the infant.

Labor and Delivery
There have been rare reports of infant respiratory distress/apnea following the administration of butorphanol tartrate injection during labor. The reports of respiratory distress/apnea have been associated with administration of a dose within two hours of delivery, use of multiple doses, use with additional analgesic or sedative drugs, or use in preterm pregnancies. (See **OVERDOSAGE, Treatment**).

In a study of 119 patients, the intravenous administration of 1 mg butorphanol tartrate during labor was associated with transient (10 to 90 minutes) sinusoidal fetal heart rate patterns, but was not associated with adverse neonatal outcomes. In the presence of an abnormal fetal heart rate pattern, butorphanol tartrate should be used with caution.

Nursing Mothers
Butorphanol has been detected in milk following administration of butorphanol tartrate injection to nursing mothers. The amount an infant would receive is probably clinically insignificant (estimated 4 mcg/L of milk in a mother receiving 2 mg IM four times a day).

Pediatric Use
Butorphanol is not recommended for use in patients below 18 years of age because safety and efficacy have not been established in this population.

Geriatric Use
The initial dose of butorphanol tartrate recommended for elderly patients is half the usual dose at twice the usual interval. Subsequent doses and intervals should be based on the patient response (see **CLINICAL PHARMACOLOGY, Individualization of Dosage**).

Due to changes in clearance, the mean half-life of butorphanol is increased by 25% in patients over the age of 65. Elderly patients may be more sensitive to its side effects.

ADVERSE REACTIONS

A total of 2446 patients were studied in butorphanol clinical trials. Approximately half received butorphanol tartrate injection with the remainder receiving butorphanol tartrate nasal spray. In nearly all cases the type and incidence of side effects with butorphanol by any route were those commonly observed with opioid analgesics.

The adverse experiences described below are based on data from short- and long-term clinical trials as well as post-marketing experience in patients receiving butorphanol by any route. There has been no attempt to correct for placebo effect or to subtract the frequencies reported by placebo treated patients in controlled trials.

The most frequently reported adverse experiences across all clinical trials with butorphanol tartrate injection and nasal spray were somnolence (43%), dizziness (19%), nausea and/or vomiting (13%). In long-term trials with the nasal spray only, nasal congestion (13%) and insomnia (11%) were frequently reported..

The following adverse experiences were reported at a frequency of 1% or greater in clinical trials, and were considered to be probably related to the use of butorphanol:

BODY AS A WHOLE: asthenia/lethargy*, headache*, sensation of heat.

CARDIOVASCULAR: VASODILATION*, PALPITATIONS.

DIGESTIVE: ANOREXIA*, CONSTIPATION*, dry mouth*, nausea and/or vomiting (13%), stomach pain.

NERVOUS: anxiety, confusion*, dizziness (19%), euphoria, floating feeling, INSOMNIA (11%), nervousness, paresthesia, somnolence (43%), TREMOR, DRUG DEPENDENCE* or WITHDRAWAL SYNDROME* (see **DRUG ABUSE AND DEPENDENCE**).

RESPIRATORY: BRONCHITIS, COUGH, DYSPNEA*, EPISTAXIS*, NASAL CONGESTION (13%), NASAL IRRITATION*, PHARYNGITIS*, RHINITIS*, SINUS CONGESTION*, SINUSITIS, UPPER RESPIRATORY INFECTION*.

SKIN AND APPENDAGES: sweating/clammy*, pruritus.

SPECIAL SENSES: blurred vision, EAR PAIN, TINNITUS*, UNPLEASANT TASTE* (also seen in short-term trials with butorphanol tartrate nasal spray).

(Reactions occurring with a frequency of 3 to 9% are marked with an asterisk (*). Reactions reported predominantly from long-term trials with butorphanol tartrate nasal spray are CAPITALIZED.)

The following adverse experiences were reported from post-marketing experience or with a frequency of less than 1%, in clinical trials, and were considered to be probably related to the use of butorphanol:

BODY AS A WHOLE: *-excessive drug effect associated with transient difficulty speaking and/or executing purposeful movements.*

CARDIOVASCULAR: hypotension, syncope.

NERVOUS: abnormal dreams, agitation, dysphoria, *-excessive drug effect associated with transient difficulty speaking and/or executing purposeful movements*, hallucinations, hostility, *vertigo.*

SKIN AND APPENDAGES: rash/hives.

UROGENITAL: impaired urination.

(Reactions reported only from post-marketing experience are *italicized.*)

The following infrequent additional adverse experiences were reported in a frequency of less than 1% of the patients studied in short-term butorphanol tartrate nasal spray trials and from post-marketing experiences under circumstances where the association between these events and butorphanol administration is unknown. They are being listed as alerting information for the physician.

BODY AS A WHOLE: edema.

CARDIOVASCULAR: chest pain, hypertension, tachycardia.

NERVOUS: *convulsion, delusion,* depression.

RESPIRATORY: *apnea,* shallow breathing.

(Reactions reported only from post-marketing experience are *italicized.*)

DRUG ABUSE AND DEPENDENCE

Butorphanol tartrate injection is listed in Schedule IV of the Controlled Substances Act (CSA).

Clinical Trial Experience

Some patients in clinical trials conducted in patients who were largely opiate-naive, had experiences typically associated with opioid abuse or dependence. These included rapid development of tolerance to the drug in which patients increased their dosage to higher levels than prescribed and reports of euphoria.

Withdrawal symptoms were identified in patients using butorphanol tartrate nasal spray in controlled clinical trials. Patients abruptly discontinuing butorphanol tartrate nasal spray after extended use or high doses were at greatest risk. Withdrawal symptoms included anxiety, agitation, tremulousness, diarrhea, chills, sweats, insomnia, confusion, incoordination, drug cravings and hallucinations.

Post-marketing Experience

Butorphanol tartrate has been associated with episodes of abuse and dependence. Of the cases received, there were more reports of abuse with the nasal spray formulation than with the injectable formulation.

Proper patient selection, dose and prescribing limitations, appropriate directions for use, and frequent monitoring are important to minimize the risk of abuse and dependence with butorphanol tartrate. Special care should be exercised in administering butorphanol to patients with a history of drug abuse or to patients receiving the drug on a repeated basis for an extended period of time.

OVERDOSAGE

Clinical Manifestations

The clinical manifestations of butorphanol overdose are those of opioid drugs in general. Consequences of overdose vary with the amount of butorphanol ingested and the degree of tolerance of the patient to the effects of opiates. The most serious symptoms are hypoventilation, cardiovascular insufficiency and/or coma.

Other symptoms of overdose may include excessive drug effect (e.g. sedation, dizziness, nausea or vomiting). This may be associated with transient difficulty speaking or executing purposeful movements. Many of the reported cases have involved people who are not tolerant to the effects of opiates and who use larger doses of butorphanol to initiate therapy (more than 2 mg butorphanol tartrate injection).

Overdose can occur due to accidental or intentional misuse of butorphanol, especially in young children who may gain access to the drug in the home.

Treatment

The management of suspected butorphanol overdosage includes maintenance of adequate ventilation, peripheral perfusion, normal body temperature, and protection of the airway. Patients should be under continuous observation with adequate serial measures of mental state, responsiveness and vital signs. Oxygen and ventilatory assistance should be available with continual monitoring by pulse oximetry if indicated. In the presence of coma, placement of an artificial airway may be required. An adequate intravenous portal should be maintained to facilitate treatment of hypotension associated with vasodilation.

The use of a specific opioid antagonist such as naloxone should be considered. As the duration of butorphanol action usually exceeds the duration of action of naloxone, repeated dosing with naloxone may be required.

In managing cases of suspected butorphanol overdosage, the possibility of multiple drug ingestion should always be considered.

DOSAGE AND ADMINISTRATION

Factors to be considered in determining the dose are age, body weight, physical status, underlying pathological condition, use of other drugs, type of anesthesia to be used, and surgical procedure involved. Use in the elderly, patients with hepatic or renal disease or in labor requires extra caution (see **PRECAUTIONS** and **CLINICAL PHARMACOLOGY, Individualization of Dosage**). The following doses are for patients who do not have impaired hepatic or renal function and who are not on CNS active agents.

Use for Pain

Intravenous: The usual recommended single dose for IV administration is 1 mg repeated every three to four hours as necessary. The effective dosage range, depending on the severity of pain, is 0.5 mg to 2 mg repeated every 3 to 4 hours.

Intramuscular: The usual recommended single dose for IM administration is 2 mg in patients who will be able to remain recumbent, in the event drowsiness or dizziness occurs. This may be repeated every 3 to 4 hours as necessary. The effective dosage range depending on the severity of pain is 1 mg to 4 mg repeated every 3 to 4 hours. There are insufficient clinical data to recommend single doses above 4 mg.

Use as Preoperative/Preanesthetic Medication

The preoperative medication dosage of butorphanol tartrate injection should be individualized (see **CLINICAL PHARMACOLOGY, Individualization of Dosage**). The usual adult dose is 2 mg IM, administered 60 to 90 minutes before surgery. This is approximately equivalent in sedative effect to 10 mg morphine or 80 mg meperidine.

Use in Balanced Anesthesia

The usual dose of butorphanol tartrate injection is 2 mg IV shortly before induction and/or 0.5 mg to 1 mg IV in increments during anesthesia. The increment may be higher, up to 0.06 mg/kg (4 mg/70 kg), depending on previous sedative, analgesic, and hypnotic drugs administered. The total dose of butorphanol tartrate will vary; however, patients seldom require less than 4 mg or more than 12.5 mg (approximately 0.06 to 0.18 mg/kg).

Labor

In patients at full term in early labor a 1 to 2 mg dose of butorphanol tartrate IV or IM may be administered and repeated after 4 hours. Alternative analgesia should be used for pain associated with delivery or if delivery is expected to occur within 4 hours.

If concomitant use of butorphanol tartrate with drugs that may potentiate its effects is deemed necessary (see **Drug Interactions** in **PRECAUTIONS** section) the lowest effective dose should be employed.

Safety and Handling

Butorphanol tartrate injection is supplied in sealed delivery systems that have a low risk of accidental exposure to health care workers. Ordinary care should be taken to avoid aerosol generation while preparing a syringe for use. Following skin contact, rinsing with cool water is recommended.

The disposal of Schedule IV controlled substances must be consistent with State and Federal Regulations.

HOW SUPPLIED

Butorphanol Tartrate Injection USP for IM or IV use is available as follows:

NDC 55390-183-01 - 1 mg/mL, 1 mL vial, carton of 10.

NDC 55390-184-01 - 2 mg/mL, 1 mL vial, carton of 10.

NDC 55390-184-02 - 4 mg/2 mL, 2 mL vial, carton of 10.

NDC 55390-185-10 - 2 mg/mL, 10 mL multiple dose vial, individually boxed.

Store at room temperature, 15° to 30°C (59° to 86°F).

Parenteral drug products should be inspected visually for particulate matter and discoloration prior to administration, whenever solution and container permit.

Protect from light.

Rx ONLY.

Manufactured for:
Bedford Laboratories™
Bedford, OH 44146

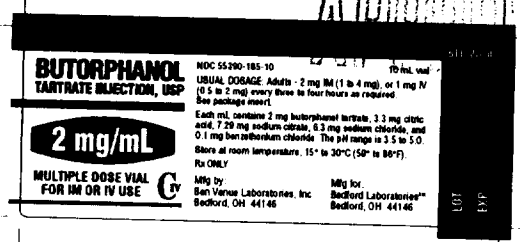
Manufactured by:
Ben Venue Laboratories
Bedford, OH 44146

June 1998 BTP-P00

AUG 12 1998

Keyline does not print

APPROVED

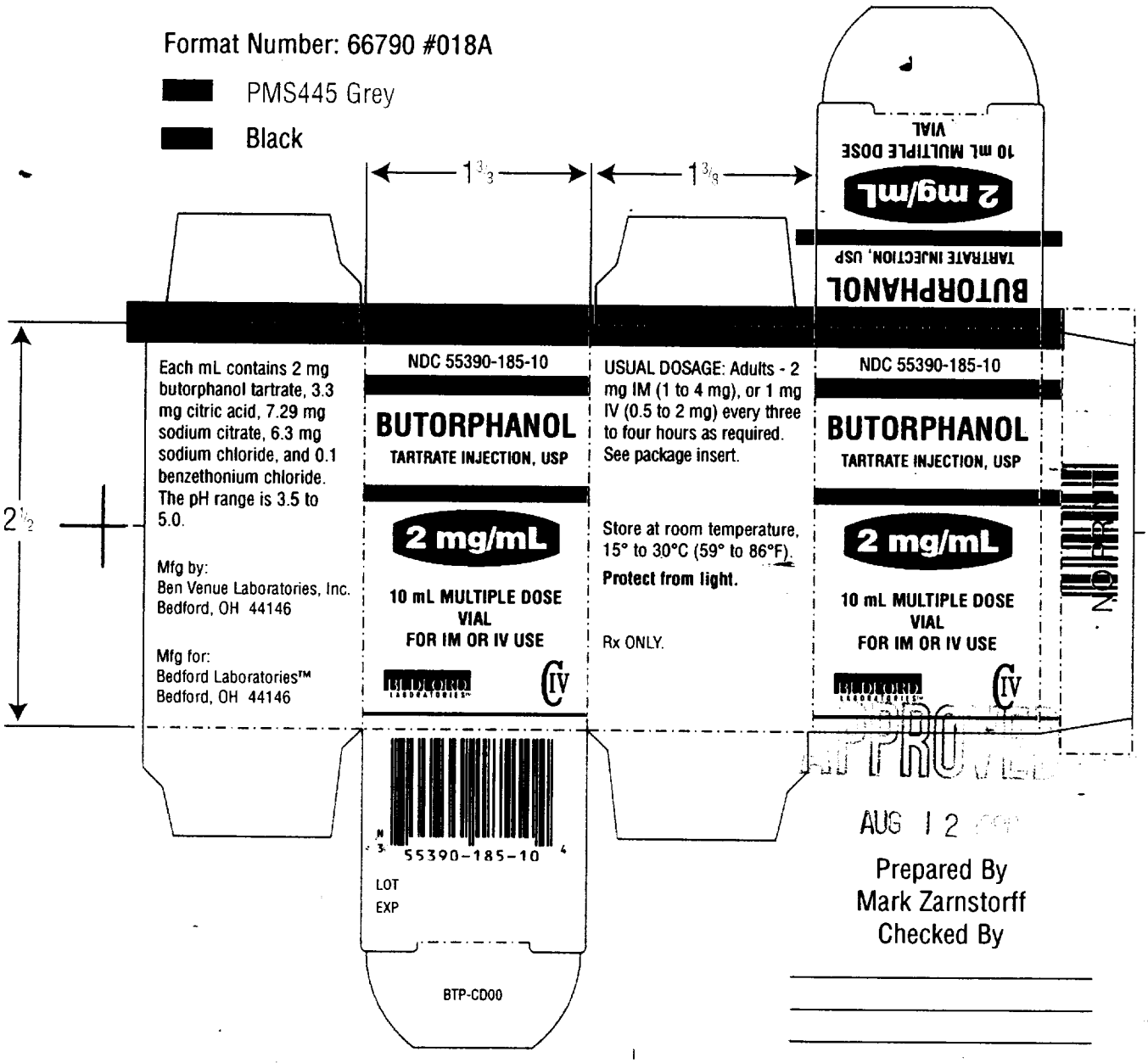


Format: 66533 #129B 1.0" x 2.5"
PMS Black, PMS 445 Gray

Format Number: 66790 #018A

PMS445 Grey

Black



AUG 12

Prepared By
Mark Zarnstorff
Checked By

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

75046

CHEMISTRY REVIEW(S)

DIVISION REVIEW SUMMARY

ANDA: 75-046

DRUG PRODUCT: Butorphanol Tartrate

FIRM: Bedford Labs.

DOSAGE FORM: Injection for IV or IM

STRENGTH: 2 mg/mL (10 mL MDV)

CGMP STATEMENT/EIR UPDATE STATUS:
Acceptable, dated 7/15/97. ~~Awaiting EER update.~~ Acceptable 8/4/98.

BIO INFORMATION:
Waiver granted, see bio letter dated 5/20/97.

VALIDATION
N/A

STABILITY
Accelerated stability studies data (40°C) for lot no. 810-49-0001 are included. Also, 12 month room temperature stability data are appended. Samples were stored in the upright and inverted positions. Based on the stability data submitted the requested 24 months expiry will be granted.

The container/closure system used is described in the container section of the application.

LABELING
Acceptable. See review dated 7/17/98.

STERILIZATION VALIDATION
Acceptable.

SIZE OF BIO/STABILITY BATCHES
Butorphanol Tartrate is synthetized by DMF
DMF was reviewed and found acceptable on 4/8/98.

Lot no. 810-49-0001 liters vials was manufactured for demonstration purposes. A total of units were sterilized.

PROPOSED PRODUCTION BATCH

A blank manufacturing batch record for the proposed production batch size of liters/ vials is appended.

RECOMMENDATION:

Recommend approval of generic drug product Butorphanol Tartrate USP, 2 mg/mL in 10 mL MDV.

SIGNATURE: DATE: April 9, 1998

1. CHEMISTRY REVIEW NO. 3

2. ANDA 75-046

3. NAME AND ADDRESS OF APPLICANT
Bedford Laboratories
300 Northfield Road
Bedford, Ohio 44146

4. BASIS OF SUBMISSION
To the best of the applicant's knowledge, the RLD has no patents and marketing exclusivities in effect.

5. SUPPLEMENT(s)
N/A

6. PROPRIETARY NAME

7. NONPROPRIETARY NAME

8. SUPPLEMENT PROVIDE FOR:
N/A

9. AMENDMENTS AND OTHER DATES:

December 30, 1996 --	Original Submission
February 24, 1997--	Acknowledgement receipt
February 27, 1997--	New correspondence--bio
March 27, 1997--	Micro review--deficient
April 15, 1997--	Labeling review--deficient
May 20, 1997--	Bio review--acceptable
July 11, 1997--	Deficiency letter
October 31, 1997--	Amendment
February 27, 1998--	Deficiency letter
April 2, 1998--	Amendment
June 12, 1998--	Amendment
June 30, 1998--	Amendment
July 8, 1998--	Amendment
July 13, 1998--	Amendment
July 17, 1998--	Amendment

10. PHARMACOLOGICAL CATEGORY
Analgesic

11. Rx or OTC
Rx

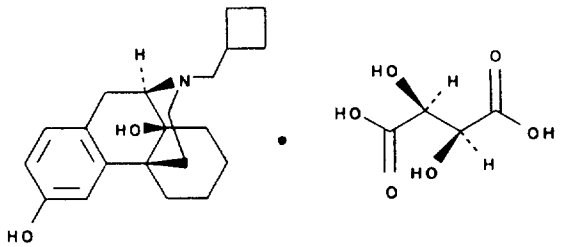
12. RELATED Drug Master Files

13. DOSAGE FORM
Injection for IV or IM

14. POTENCY
2 mg/mL (10 mL MDV)

15. CHEMICAL NAME AND STRUCTURE

Butorphanol Tartrate USP



$C_{21}H_{29}NO_2 . C_4H_6O_6$; M.W. = 477.56

(-)-17-(Cyclobutylmethyl)morphinan-3,14-diol *D*-(-)-tartrate (1:1) (salt). CAS [58786-99-5]

16. RECORDS AND REPORTS
N/A

17. COMMENTS
Responses to our deficiency letter dated February 27, 1998, can be found **bolded** under each distinctive section of this chemistry review.

18. CONCLUSIONS AND RECOMMENDATIONS
Recommend approval letter to issue.

19. REVIEWER:
Edwin Ramos

DATE COMPLETED:
April 9, 1998

/S/

8/5/98

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

75046

MICROBIOLOGY REVIEW

Microbiology Comments to be Provided to the Applicant

ANDA: 75-046 APPLICANT: Bedford Laboratories™

DRUG PRODUCT: Butorphanol Tartrate Injection USP, 2 mg/mL, 10 mL Multiple-Dose Vials

A. Microbiology Deficiencies:

1. Please provide a Microbial Ingress Container/Closure Integrity Test for the container/closure system that will be used for the product, Butorphanol Tartrate Injection USP, i.e., 20 mm finish 10 mL amber vial.

2. Please include the Bacterial Endotoxin Test in the stability protocol at 30 months if the expiration date is extended for the subject drug product.

3. Please include the Antimicrobial Preservative Effectiveness Test (APET) in the stability protocol for first three production lots.

B. In addition to responding to the deficiencies presented above, please note and acknowledge the following comments in your response:

The "lots" referred to in the post approval commitment should include all sizes and strengths of the subject drug product.

Please clearly identify your amendment to this facsimile as "RESPONSE TO MICROBIOLOGY DEFICIENCIES".

Sincerely yours,

/S/

Frank Q. Holcombe, Jr., Ph.D.
Director
Division of Chemistry II
Office of Generic Drugs
Center for Drug Evaluation and Research

[redacted]

OFFICE OF GENERIC DRUGS, HFD-640
Microbiologist's Review #1
March 27, 1997

A. 1. **ANDA** 75-046

APPLICANT Bedford Laboratories™

2. PRODUCT NAMES: Butorphanol Tartrate Injection USP

3. DOSAGE FORM AND ROUTE OF ADMINISTRATION: 2 mg/mL, 10 mL Multiple-Dose Vials, Preserved, Intravenous, Intramuscular

4. METHOD(S) OF STERILIZATION:

5. PHARMACOLOGICAL CATEGORY: Narcotic Analgesic

B. 1. DATE OF INITIAL SUBMISSION: December 30, 1996
Subject of this Review (Received December 31, 1996)

2. DATE OF AMENDMENT: None

3. RELATED DOCUMENTS: NDA 17-857
DMF
DMF
DMF

4. ASSIGNED FOR REVIEW: 3/26/97

C. REMARKS: The subject drug is manufactured at the Ben Venue, Bedford, Ohio pharmaceutical facility.

D. CONCLUSIONS: The submission is not recommended for approval on the basis of sterility assurance. Specific comments are provided

/S/ 3/27/97
Andrea S. High, Ph. D.

3/31/97

cc: Original **ANDA**
Duplicate ANDA
Division Copy
Field Copy
Drafted by A. High, HFD 640 x:wp\microrev\75-046
Initialed by F. Fang or F. Holcombe, Jr.

OFFICE OF GENERIC DRUGS, HFD-640

Microbiologist's Review #2

April 23, 1998

A. 1. **ANDA** 75-046

APPLICANT Bedford Laboratories™

2. **PRODUCT NAMES**: Butorphanol Tartrate Injection USP

3. **DOSAGE FORM AND ROUTE OF ADMINISTRATION**: 2 mg/mL, 10 mL Multiple-Dose Vials, Preserved, Intravenous, Intramuscular

4. **METHOD(S) OF STERILIZATION**:

5. **PHARMACOLOGICAL CATEGORY**: Narcotic Analgesic

B. 1. **DATE OF INITIAL SUBMISSION**: December 30, 1996 (Received December 31, 1996)

2. **DATE OF AMENDMENT**: October 31, 1997
Subject of this Review (Received, November 3, 1997)

3. **RELATED DOCUMENTS**: None

4. **ASSIGNED FOR REVIEW**: 4/23/98

C. **REMARKS**: The subject amendment provides for the response to the microbiology deficiencies in the correspondence dated July 11, 1997.

D. **CONCLUSIONS**: The submission is recommended for approval on the basis of sterility assurance. Specific comments are provided

/S/ 4/23/98

Andrea S. High, Ph. D.

4/30/98

cc: Original **ANDA**
Duplicate ANDA
Division Copy
Field Copy
Drafted by A. High, HFD 640 x:wp\microrev\75-046a
Initialed by F. Fang or F. Holcombe, Jr.

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

75046

BIOEQUIVALENCY REVIEW(S)

JUN 12 1997

Butorphanol Tartrate
2 mg/mL injection (10-mL MD vial)
ANDA #75-046
Reviewer: A.P.Patel
File: x:/wpfile/biofinal/75046W.d96

Bedford Labs.
Bedford, OH
Submitted:
Dec. 30, 1996

REVIEW OF A WAIVER REQUEST

Background:

The sponsor has submitted an ANDA in support of its test product butorphanol tartrate injection 2 mg/mL in 10-mL multiple dose (MD) vials. Waiver of in vivo demonstration of bioequivalence is requested. The reference listed drug (RLD) is Stadol® Injection (NDA #17-857, approved 8/22/78, Apothecon).

Introduction:
Butorphanol is used in the management of pain when the use of an opioid analgesic is appropriate. It is also used in preoperative or preanesthetic medication, as a supplement to balanced anaesthesia, and for the relief of pain during labor.

Comments:

1. The test product and RLD are identical with regard to conditions of use, dosage form (sterile injectable solution), active ingredient (butorphanol tartrate), routes of administration (IV or IM), and strength (2 mg/mL).

2. Table 1 shows the comparative formulations of the test product and RLD.

3. The sponsor is requesting waiver of in vivo bioequivalence study requirements according to 21 CFR Part 320.22(b)(1) since the proposed test product is a parenteral solution intended solely for administration by injection and contains the same active and inactive ingredients in the same concentration as the RLD.

4. NOTE: The typographical error on page 9 under side by side comparison of excipients for proposed drug, "sodium chloride , USP, 6.4 mg (7.29 mg as dihydrate)" and on page 77 under composition statement, "sodium chloride, USP 6.3 mg."

For Internal Use Only
On the carton label sodium chloride is listed as 6.3 mg and on the insert sodium chloride is listed as 6.4 mg, for both the RLD and sponsor (Labeling reviewer is aware of this discrepancy).

Recommendation:

The Division of Bioequivalence agrees that the information submitted by Bedford Labs. demonstrates that butorphanol tartrate injection 2 mg/mL (10-mL multiple dose vials) falls under 21 CFR Section 320.22(b)(1) of the Bioavailability/Bioequivalence Regulations. The waiver of in vivo bioequivalence study for the test product butorphanol tartrate injection 2 mg/mL (10-mL multiple dose vials) is granted. From the bioequivalence point of view, the test product butorphanol tartrate injection 2 mg/mL (10-mL multiple dose vials, Bedford Labs.) is deemed Bioequivalent to Stadol® Injection manufactured by Apothecon.

The firm should be informed of the recommendation and comment #4.

/S/ 6/8/97

A.P.Patel
Division of Bioequivalence
Review Branch III

RD INITIALED RMHATRE
FT INITIALED RMHATRE /S/ Date: 6/03/97
Ramakant M. Mhatre, Ph.D.
Chief, Branch III
Division of Bioequivalence

Concur
for Nicholas M. Fleischer, Ph.D. /S/ Date: 6/12/97
Director
Division of Bioequivalence

cc: 75-046 (original), A.P.Patel, HFD-650 (Director), Division File, Drug File

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

75046

ADMINISTRATIVE DOCUMENTS

REVIEW OF PROFESSIONAL LABELING
DIVISION OF LABELING AND PROGRAM SUPPORT
LABELING REVIEW BRANCH

ANDA Number: **75-046** Date of Submission: **December 30, 1996**

Applicant's Name: **Bedford Laboratories**

Established Name: **Butorphanol Tartrate Injection USP, 2 mg/mL, 10 mL vial**

Labeling Deficiencies:

1. GENERAL COMMENTS:

   We note you have submitted a combined insert with ANDA 75-045. Please be advised these two applications must be approved simultaneously or the labeling must be revised.

2. CONTAINER (2 mg/mL - 10 mL)

   a. Revise the expression of strength to read as follows:

      2 mg/mL

   b. Include the pH of the solution.

3. CARTON (1 x 10 mL)

   See comments under CONTAINER.

4. INSERT

   a. See GENERAL COMMENT above.

   b. DESCRIPTION

      i. To be in accord with USP 23, revise the molecular weight to read "477.56" rather than

      ii. Revise the second paragraph to read as follows:

      ...acidic. It melts between 217° and 219°, with decomposition. It is sparingly soluble in water...

iii. Revise paragraph three to read as follows:

...administration. Each mL of solution contains 1 or 2 mg of butorphanol tartrate. In addition, each mL contains 3.3 mg of...

iv. Include the pH.

b. CLINICAL PHARMACOLOGY

i. Pharmacokinetics

A) Delete the " information from Figure 1 and the table and revise the title of the table to read "...Parameters of Intravenous Butorphanol...". In addition, revise the subscripts accordingly.

B) Paragraph six following table 1 - Revise to read:

Butorphanol pharmacokinetics in...

ii. Individualization of Dosage, paragraph two - ...sections in PRECAUTIONS).

c. WARNINGS

Patients Dependent on Narcotics, first sentence - ...use in patients...

d. ADVERSE REACTIONS

Insert the following text to appear as the last sentence of paragraph three:

In long-term trials with the nasal spray only, nasal congestion (13%) and insomnia (11%) were frequently reported.

e. DOSAGE AND ADMINISTRATION

Revise the second sentence of paragraph one to read as follows:

Use in the elderly,...

f. HOW SUPPLIED

Revise the penultimate entry to read:

...4 mg/2 mL, 2 mL vial...

Please revise your container labels, carton and insert labeling, as instructed above, and submit final printed labels and labeling.

Please note that we reserve the right to request further changes in your labels and/or labeling based upon changes in the approved labeling of the listed drug or upon further review of the application prior to approval.

To facilitate review of your next submission, and in accordance with 21 CFR 314.94(a)(8)(iv), please provide a side-by-side comparison of your proposed labeling with your last submission with all differences annotated and explained.

Jerry Phillips
Director
Division of Labeling and Program Support
Office of Generic Drugs
Center for Drug Evaluation and Research

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

75046

CORRESPONDENCE

ANDA 75-046

JUN 16 1997

Bedford Laboratories
Division of Ben Venue Laboratories, Inc.
Attention: Robert V. Kasubick, Ph.D.
270 Northfield Road
Bedford OH 44146

Dear Sir:

Reference is made to your abbreviated new drug application submitted pursuant to Section 505 (j) of the Federal Food, Drug and Cosmetic Act for Butorphanol Tartrate Injection USP, 2 mg/mL, 10 mL multiple-dose vials.

The Division of Bioequivalence has completed its review and has no further questions at this time.

Please note that the bioequivalency comments expressed in this letter are preliminary. The above bioequivalency comments may be revised after review of the entire application, upon consideration of the chemistry, manufacturing and controls, microbiology, labeling or other scientific or regulatory issues. A revised determination may require additional information and/or studies, or may conclude that the proposed formulation is not approvable.

Sincerely yours,

/S/

Nicholas Fleischer, Ph.D.
Director, Division of Bioequivalence
Office of Generic Drugs
Center for Drug Evaluation and Research

ANDA 75-046

Bedford Laboratories
Division of Ben Venue Laboratories, Inc.
Attention: Robert V. Kasubick, Ph.D.
270 Northfield Road
Bedford, OH 44146

FEB 24 1997

Dear Sir:

We acknowledge the receipt of your abbreviated new drug application submitted pursuant to Section 505(j) of the Federal Food, Drug and Cosmetic Act.

NAME OF DRUG: Butorphanol Tartrate Injection USP, 2 mg/mL, 10 mL multiple-dose vials

DATE OF APPLICATION: December 30, 1996

DATE OF RECEIPT: December 31, 1996

We will correspond with you further after we have had the opportunity to review the application.

Please provide a side-by-side, qualitative and quantitative comparison of the formulation for your proposed drug product with that of the reference listed drug product in the bioequivalence section of your application. Please include this information in future submissions for parenteral drug products [21 CFR 320.22(b)(1)(i)&(ii)].

Please identify any communications concerning this application with the ANDA number shown above.

Should you have questions concerning this application, contact:

Tim Ames
Project Manager
(301) 594-0305

Sincerely yours,

/S/

Jerry Phillips 2/24/97
Director
Division of Labeling and Program Support
Office of Generic Drugs
Center for Drug Evaluation and Research

BEDFORD
LABORATORIES™

July 17, 1998

Office of Generic Drugs
Center for Drug Evaluation and Research
Food and Drug Administration
Metro Park II
7500 Standish Place, Room 150
Rockville, MD 20855

NDA ORIG AMENDMENT
N /AF

Re: **ANDA 75-046\Telephone Amendment**
Product: **Butorphanol Tartrate Injection, USP, 2 mg/mL, 10 mL multiple dose vials**

Dear Sir:

We wish to amend our unapproved Abbreviated New Drug Application, ANDA 75-046, for Butorphanol Tartrate Injection, USP, 2 mg/mL, 10 mL multiple dose vials to remove the deficiencies cited in the telephone communication of July 17, 1998.

We commit to adding the phrase "20 mg/10 mL" to the front panel under the dosage oval and above the phrase "MULTIPLE DOSE VIAL". This change will be enacted prior to any distribution of the product.

We trust this meets with your approval. If the Agency has any further questions or comments, we welcome direct contact at (440) 232-3320, ext. 293 or ext. 333.

Sincerely,
for Bedford Laboratories™

Shahid Ahmed
Director, Regulatory Affairs
Ben Venue Laboratories, Inc.

RECEIVED
JUL 20 1998
GENERIC DRUGS

A DIVISION OF BEN VENUE LABORATORIES, INC.
300 Northfield Road • Bedford, Ohio 44146 • (440) 232-3320 • Fax (440) 232-6264

BEDFORD
LABORATORIES™

Labeling received
dated 7/17/98
gl

July 13, 1998

NDA ORIG AMENDMENT
N / AF

Office of Generic Drugs
Center for Drug Evaluation and Research
Food and Drug Administration
Metro Park II
7500 Standish Place, Room 150
Rockville, MD 20855

Re: **ANDA 75-046\Telephone Amendment**
Product: **Butorphanol Tartrate Injection, USP, 2 mg/mL, 10 mL multiple dose vials**

Dear Sir/Madame:

We wish to amend our unapproved Abbreviated New Drug Application, ANDA 75-046, for Butorphanol Tartrate Injection, USP, 2 mg/mL, 10 mL multiple dose vials to remove the deficiencies cited in the telephone communication of July 2, 1998.

Labeling Deficiencies

Please find enclosed the 12 final printed vial labels and package insert labeling committed to by Bedford Laboratories™ in our previous facsimile response of July 8, 1998. The package insert has ink markings on the backside of the insert. These markings are a function of this particular printing and will not appear on future commercial labeling.

We trust this meets with your approval. If the Agency has any further questions or comments, we welcome direct contact at (440) 232-3320, ext. 333 or (440) 439-6398 (facsimile).

Sincerely,
for Bedford Laboratories™

Shahid Ahmed
Director, Regulatory Affairs
Ben Venue Laboratories, Inc.

RECEIVED
JUL 14 1998
GENERIC DRUGS

A DIVISION OF BEN VENUE LABORATORIES, INC.
300 Northfield Road • Bedford, Ohio 44146 • (440) 232-3320 • Fax (440) 232-6264

orig

BEDFORD LABORATORIES™

ORIG AMENDMENT

N/AF

July 8, 1998

Labeling Review
drafted 7/17/98
CA. Uzzo

Office of Generic Drugs
Center for Drug Evaluation and Research
Food and Drug Administration
Metro Park II
7500 Standish Place, Room 150
Rockville, MD 20855

Re: **ANDA 75-046 \Telephone Amendment**
Product: **Butorphanol Tartrate Injection, USP - 2 mg/mL, 10 mL multiple dose vials**

Dear Sir/Madame:

We wish to amend our unapproved Abbreviated New Drug Application, ANDA 75-046, for Butorphanol Tartrate Injection, USP, 2 mg/mL, 10 mL multiple dose vials to remove the deficiencies cited in the telephone communication of July 2, 1998.

Labeling Deficiencies

> Please find enclosed a copy of the computer generated container labels reflecting the change in position of the controlled substance symbol. As requested, the symbol has been moved from the side panel to the main panel. Bedford Laboratories™ commits to provide you the 12 final printed vial labels and package insert labeling by next week.

We trust this meets with your approval. If the Agency has any further questions or comments, we welcome direct contact at (440) 232-3320, ext. 333 or (440) 439-6398 (facsimile).

Sincerely,
for Bedford Laboratories™

for Rao

Shahid Ahmed
Director, Regulatory Affairs
Ben Venue Laboratories, Inc.

RECEIVED
JUL 09 1998
GENERIC DRUGS

A DIVISION OF BEN VENUE LABORATORIES, INC.
300 Northfield Road • Bedford, Ohio 44146 • (440) 232-3320 • Fax (440) 232-6264

BEDFORD LABORATORIES™

ORIG AMENDMENT
N/AF
labeling in 20d
dtd 7/17/98

June 30, 1998

Office of Generic Drugs
Center for Drug Evaluation and Research
Food and Drug Administration
Metro Park II
7500 Standish Place, Room 150
Rockville, MD 20855

Re: **ANDA 75-046 \Telephone Amendment**
Product: **Butorphanol Tartrate Injection, USP - 2 mg/mL, 10 mL multiple dose vials**

Dear Sir/Madame:

We wish to amend our unapproved Abbreviated New Drug Application, ANDA 75-046, for Butorphanol Tartrate Injection, USP, 2 mg/mL, 10 mL multiple dose vials to remove the deficiencies cited in the facsimile communication of June 25, 1998.

Labeling Deficiencies

Please find enclosed a copy of final printed label and a side-by-side comparison of the insert versus that last submitted. Also, enclosed are the computer generated container labels reflecting the change to the storage temperature range and controlled substance symbol to improve legibility. Bedford Laboratories™ commits to provide you the 12 final printed vial labels and package insert labeling by next week.

Bedford Laboratories™ also commits to changing the storage temperature range on the carton labeling prior to marketing.

We trust this meets with your approval. If the Agency has any further questions or comments, we welcome direct contact at (440) 232-3320, ext. 333 or (440) 439-6398 (facsimile).

Sincerely,
for Bedford Laboratories™

Shahid Ahmed
Director, Regulatory Affairs
Ben Venue Laboratories, Inc.

RECEIVED
JUL 09 1998
GENERIC DRUGS

A DIVISION OF BEN VENUE LABORATORIES, INC.
300 Northfield Road • Bedford, Ohio 44146 • (440) 232-3320 • Fax (440) 232-6264

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Labeling review
Acknowl. 6/25/98
[illegible]

NDA ORIG AMENDMENT

N/AF

June 12, 1998

Office of Generic Drugs
Center for Drug Evaluation and Research
Food and Drug Administration
Metro Park II
7500 Standish Place, Room 150
Rockville, MD 20855

Re: **ANDA 75-046 Labeling Deficiencies**
Product: **Butorphanol Tartrate Injection, USP - 2 mg/mL, 10 mL multiple dose vials**

Dear Sir/Madame:

We wish to amend our unapproved Abbreviated New Drug Application, ANDA 75-046, for Butorphanol Tartrate Injection, USP, 2 mg/mL, 10 mL multiple dose vials to remove the deficiencies cited in the facsimile communication of May 8, 1998.

Labeling Deficiencies

> Please find enclosed 12 copies of final printed labels, carton and insert labeling. The label and carton is being provided due to a change in storage temperature to match the revised insert. Also included are side-by-side comparisons of the current proposed labels cartons, and insert versus that last submitted.

We trust this meets with your approval. If the Agency has any further questions or comments, we welcome direct contact at (440) 232-3320, ext. 333 or (440) 439-6398 (facsimile).

Sincerely,
for Bedford Laboratories™

Shahid Ahmed
Director, Regulatory Affairs
Ben Venue Laboratories, Inc.

RECEIVED
JUN 12 1998
GENERIC DRUGS

BEDFORD
LABORATORIES™

labeling rewritten 5/8/98 RLD PI changed AND insert needs revision Alaya

ORIG AMENDMENT
NDA/AM

April 2, 1998

shared insert with ANDA 75-045

Office of Generic Drugs
Center for Drug Evaluation and Research
Food and Drug Administration
Metro Park II
7500 Standish Place, Room 150
Rockville, MD 20855

Re: ANDA 75-046/Minor Amendment
Product: Butorphanol Tartrate Injection, USP - 2 mg/mL, 10 mL MDV

Dear Sir/Madame:

We wish to amend our unapproved Abbreviated New Drug Application, ANDA 75-046, for Butorphanol Tartrate Injection, USP, 2 mg/mL, 10 mL MDV, to remove the deficiencies cited in the facsimile communication of February 27, 1998.

The number associated with the response given below corresponds to the number identifying the deficiencies in the communication.

A. Chemistry Deficiencies

1. holder of DMF has responded to the Agency regarding their deficiencies, as stated in the letter presented in Attachment I. Bedford Laboratories™ acknowledges that this application cannot be approved until these deficiencies are answered satisfactorily.

2. Please refer to Attachment II for a revised Components and Composition table indicating the amount of salt which is equivalent to the free base.

B. Labeling Deficiencies

Please refer to Attachment III for 12 copies of final printed labels, carton and insert labeling. Also located in this attachment are side-by-side comparisons of the current proposed labels and labeling versus that last submitted.

We trust this meets with your approval. If the Agency has any further questions or comments, we welcome direct contact at (440) 232-3320, ext. 333 or (440) 439-6398 (facsimile).

RECEIVED
APR 0 3 1998
4-3-98
GENERIC DRUGS

A DIVISION OF BEN VENUE LABORATORIES, INC.
300 Northfield Road • Bedford, Ohio 44146 • (216) 232-3320 • Fax (216) 232-6264

BEDFORD
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Sincerely,
for Bedford Laboratories™

Shahid Ahmed
Director, Regulatory Affairs
Ben Venue Laboratories, Inc.

BEDFORD LABORATORIES™

Hartley Brantley 2/14/97

Labeling Review completed. Chulquist for Durette 4/15/97

December 30, 1996

RECEIVED DEC 31 1996 GENERIC DRUGS

RECEIVED GENERIC DRUGS

Office of Generic Drugs
Center for Drug Evaluations and Research
Metro Park II
7500 Standish Place, Room 150
Rockville, MD 20855

Re: **Abbreviated New Drug Application**
Product: **Butorphanol Tartrate Injection, USP - 2 mg/mL, 10 mL vials MDV**

Dear Sir/Madam:

In accordance with Section 505 (j)(1) of the Federal Food, Drug and Cosmetic Act, Bedford Laboratories™ is submitting in triplicate (an archival copy, a review copy and a field copy) an Abbreviated New Drug Application for Butorphanol Tartrate Injection, USP, 2 mg/mL, 10 mL vials (MDV). Please note that the field copy is being sent directly to the FDA District Office in Cincinnati, Ohio.

The drug products subject to this application contains the information required by Section 505 (j)(2)(a)(i), (ii)(I), (iv), (v) and (vi). The application is provided in the format suggested by your office, and contains a copy of the package insert of the "listed drug's" (Apothecon's Stadol®, NDA 17-857) as well as copies of the relevant pages of the **Approved Prescription Drug Products List with Therapeutic Equivalence Evaluations.**

In accordance with Title 21 CFR 320.22, Bedford Laboratories™ requests a waiver of the requirement for submission of evidence demonstrating the *in vivo* bioavailability/bioequivalence for the drug products that are the subject of our application (Butorphanol Tartrate Injection, USP, 2 mg/mL, 10 mL vials MDV). The drug products are solutions intended solely for intramuscular or intravenous administration and contain an active ingredient in the same solvent and concentrations as drug products that are the subject of an approved New Drug Application (Apothecon's Stadol®, NDA 17-857).

Bedford Laboratories™ certifies that the methods used in, and the facilities and controls used for the manufacture, processing, packaging and holding of the drug products are in conformity with current Good Manufacturing Practices in accordance with Title 21 CFR 210 and 211. Ben Venue Laboratories, Inc., signed statement is provided in Section IX (Manufacturing Facility) Subsection C (cGMP Certification).

Three copies of the analytical methods and method validations are enclosed in this package, also.

One copy of the Microbiological Validation, along with the drug products' specifications, stability

protocols and the package insert is enclosed separately with this application. These drug products were sterilized.

If the Agency has any comments or further requests or if we could be of any assistance in your review, we welcome direct and immediate telephone contact at (216) 232-3320, ext. 218 or by facsimile (216) 232-2772.

Sincerely,
for Bedford Laboratories™

Thomas R. Russillo
COO and President
Ben Venue Laboratories, Inc.